

Clearly Lerner teaches that some effects of aging can be treated by decreasing the level of nitric oxide in the skin. However, it is not inevitable that Lerner teaches that each and every effect of aging or exposure to UV light can be treated in this manner. To determine the extent of Lerner's teaching, the reference must be considered as a whole. MPEP § 2141.03 instructs:

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. [emphasis added]

In this regard, Lerner also teaches, at page 2, lines 22-24, that:

Conditions characterized by the lack of or by an insufficient number of dermal or epidermal cells, e.g., melanocytes or keratinocytes, or a lack of pigmentation, are treated by reducing the level of NO in the skin.

This passage tends to lead away from the use of a NOS inhibitor to treating wrinkles, since wrinkles are not fundamentally a defect in the number of melanocytes or keratinocytes. A wrinkle is a configuration change in the surface of the skin, without specific structural alterations at the histological level. Zucchetti suggests, at column 2, lines 42-47, that wrinkles may be due to deterioration of structural proteins such as collagen. For example, Zucchetti attributes this "to the drop in production of collagen, elastin and glucosaminoglycans." Neither Zucchetti nor Lerner suggests that this type of defect can be treated by decreasing nitric oxide, by increasing proliferation of melanocytes and keratinocytes, or by altering pigmentation. Yamaguchi, teaches (i) the formation of some wrinkles are accelerated by exposure to UV-B and (ii) wrinkles can be treated with a furan derivative. Again, neither Yamaguchi nor Lerner suggest that wrinkles can be treated by decreasing nitric oxide, by increasing proliferation of melanocytes and keratinocytes, or by altering pigmentation.

Even so, the Examiner's response focuses on the broader language in Lerner and fails to account for Lerner's scientific explanation about how NOS inhibitors modulate melanocyte and keatinocyte proliferation. For example, at pages 2-3 of the most recent action, the Examiner states:

Applicants' argue that Lerner teaches treating a subset of conditions associated with aging, i.e. conditions characterized by melanocytes or keratinocytes and neither Lerner nor Zucchetti teach or suggest that wrinkles are in any way associated with unwanted proliferation or insufficient number of melanocytes or keratinocytes. This is not persuasive because

Lerner et al on page 4, first full paragraph, teach a method of treating a subject for sunburn or other exposure to ultraviolet light or for unwanted effects of aging on the skin by administering a treatment which decreases the level of nitric oxide (NO) in the skin.

Obviousness does not permit the Examiner to disregard the scientific explanation in Lerner. The Examiner merely resorts to broader language that fails to explicitly teach treating wrinkles. As a matter of law, the Examiner is required to find some support for the premise that Lerner's teachings as a whole would lead one to use a NOS inhibitor to treat wrinkles. In re Fine, 837 F2d 1071 (Fed. Cir. 1988), sets forth the basic standard. According to MPEP § 2143.01:

In *In re Fine*, the claims were directed to a system for detecting and measuring minute quantities on nitrogen compounds comprising a gas chromatograph, a converter which converts nitrogen compounds into nitric oxide by combustion, and a nitric oxide detector. The primary reference disclosed a system for monitoring sulfur compounds comprising a chromatograph, combustion means, and a detector, and the secondary reference taught nitric oxide detectors. The examiner and Board asserted that it would have been within the skill of the art to substitute one type of detector for another in the system of the primary reference, however the court found there was no support or explanation of this conclusion and reversed. [emphasis added]

The situation in In re Fine is not unlike the Examiner's obviousness rejection. Again, in In re Fine, the first reference disclosed a genus (detectors); and the second reference identified a species (a specific detector). Absent from the rejection was support for inserting the specific detector into the system in the first reference. In the present rejection, one reference discloses treating unwanted effects of aging and UV exposure. A second reference identifies wrinkles as an effect of (i) aging or (ii) UV-B exposure. However, no basis is advanced for inserting wrinkles into the first reference. Moreover, here the first reference, by explaining that the therapeutic mechanism relates to proliferation of melanocytes and keratinocytes, does not admit to the modification. Thus, a prima facie case of obviousness has not been established.

In addition, the rejection also does not establish a reasonable expectation of success for the alleged combination. As discussed above, Zucchetti characterizes wrinkles as a defect in collagen, elastin and glucosaminoglycans that can be treated with levogyre ascorbic acid (LAA). Yamaguchi characterizes UV-B accelerated wrinkles as a defect that can be treated by a furan

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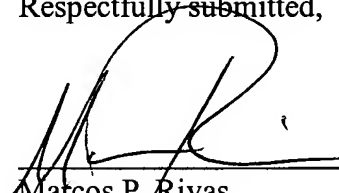
derivative. Yamaguchi does not explain how furan derivatives treat wrinkles. Lerner characterizes the use of NOS inhibitors as increasing melanocytes or keratinocytes or altering pigmentation. These disparities between the references are evidence of a lack of expectation of success.

Remington does not make up for the deficiencies in Lerner and Zucchetti. For the reasons presented herein, Applicants respectfully request that the rejections be withdrawn.

Enclosed is a \$430 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 10287-066001.

Respectfully submitted,

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